“The Challenge of Treating Type 2 Diabetic Patients with Chronic Kidney Disease”

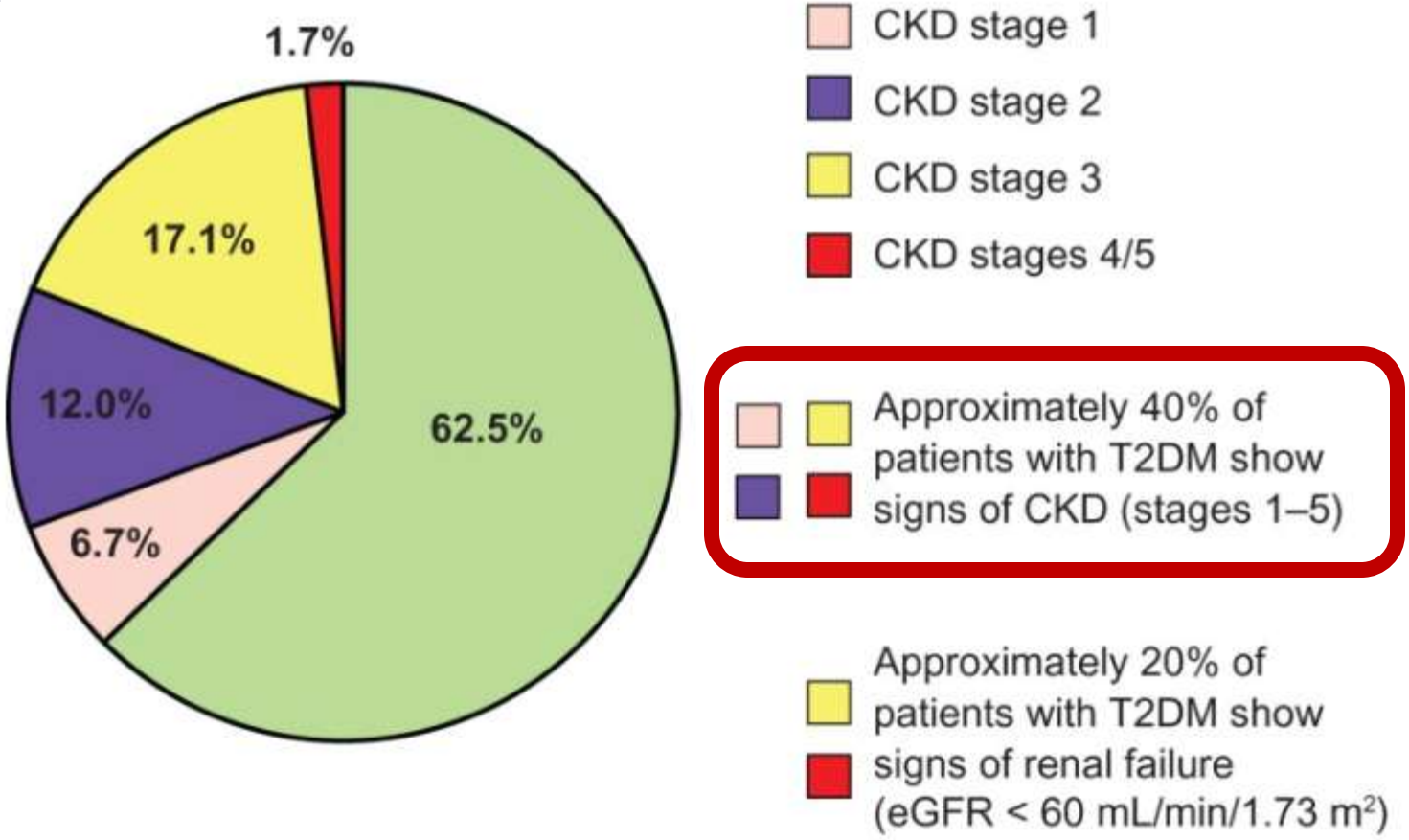
Ashraf Talaat,MD.

What I'm not Going to talk about :

- Pathogenesis.
- Biomarkers.

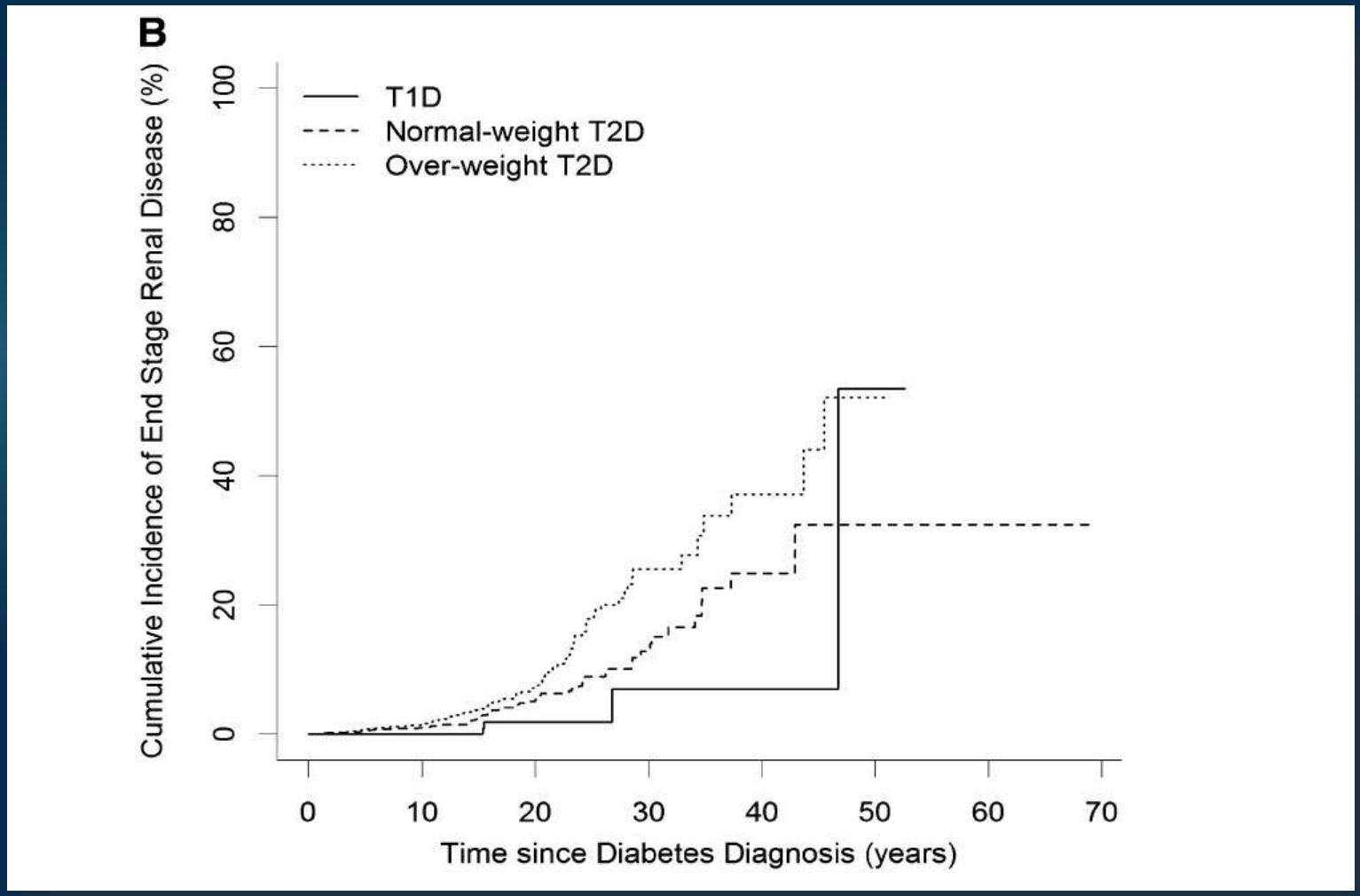
But Recent Data must be Known.

Renal Dysfunction Is Common in Patients with Type 2 Diabetes



Russo E, et al. Diabetes Metab Syndr Obes. 2013; 6: 161–170.

Young patients with T2DM had greater risks of developing ESRD compared with patients with T1DM



ESRD: End- Stage Renal Disease

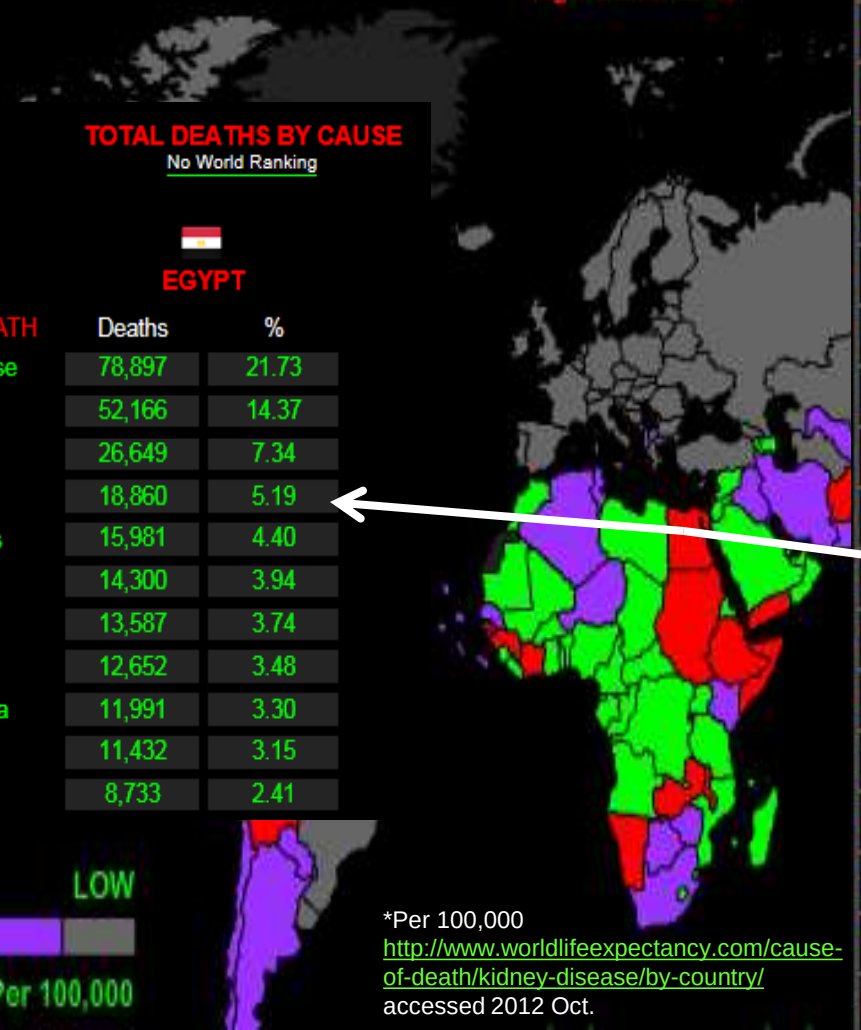
Luk AO, et al. Diabetes Care. 2014 Jan;37(1):149-57

Rate of Kidney Diseases in Egypt is 36.4* with About 5.19% Deaths

RETURN WORLD HEALTH MENU

KIDNEY DISEASE

Death Rate Per 100,000
Age Standardized



TOTAL DEATHS BY CAUSE

No World Ranking

EGYPT

TOP 50 CAUSES OF DEATH	Deaths	%
1 Coronary Heart Disease	78,897	21.73
2 Stroke	52,166	14.37
3 Liver Disease	26,649	7.34
4 Kidney Disease	18,860	5.19
5 Road Traffic Accidents	15,981	4.40
6 Hypertension	14,300	3.94
7 Low Birth Weight	13,587	3.74
8 Endocrine Disorders	12,652	3.48
9 Influenza & Pneumonia	11,991	3.30
10 Diabetes Mellitus	11,432	3.15
11 Congenital Anomalies	8,733	2.41

HIGH LOW

Death Rate Per 100,000

Rank	Country	Rate	Rank
1	EL SALVADOR	61.2	65
2	MARSHALL ISL.	60.6	66
3	AFGHANISTAN	53.3	67
4	NAURU	53.2	68
5	BOLIVIA	45.7	69
6	TUVALU	45.6	70
7	SOMALIA	44.4	71
8	HONDURAS	42.6	72
9	SUDAN	42.4	73
10	NICARAGUA	41.3	74
11	DJIBOUTI	36.4	75
12	EGYPT	36.4	76
13	THAILAND	36.2	77
14	BAHRAIN	36.2	78
15	MALAWI	35.8	79
16	FIJI	34.4	80
17	YEMEN	34.1	81
18	COTE D IVOIRE	31.8	82

*Per 100,000
http://www.worldlifeexpectancy.com/cause-of-death/kidney-disease/by-country/
accessed 2012 Oct.

meeting report

http://www.kidney-international.org

Burden of chronic kidney disease: North Africa

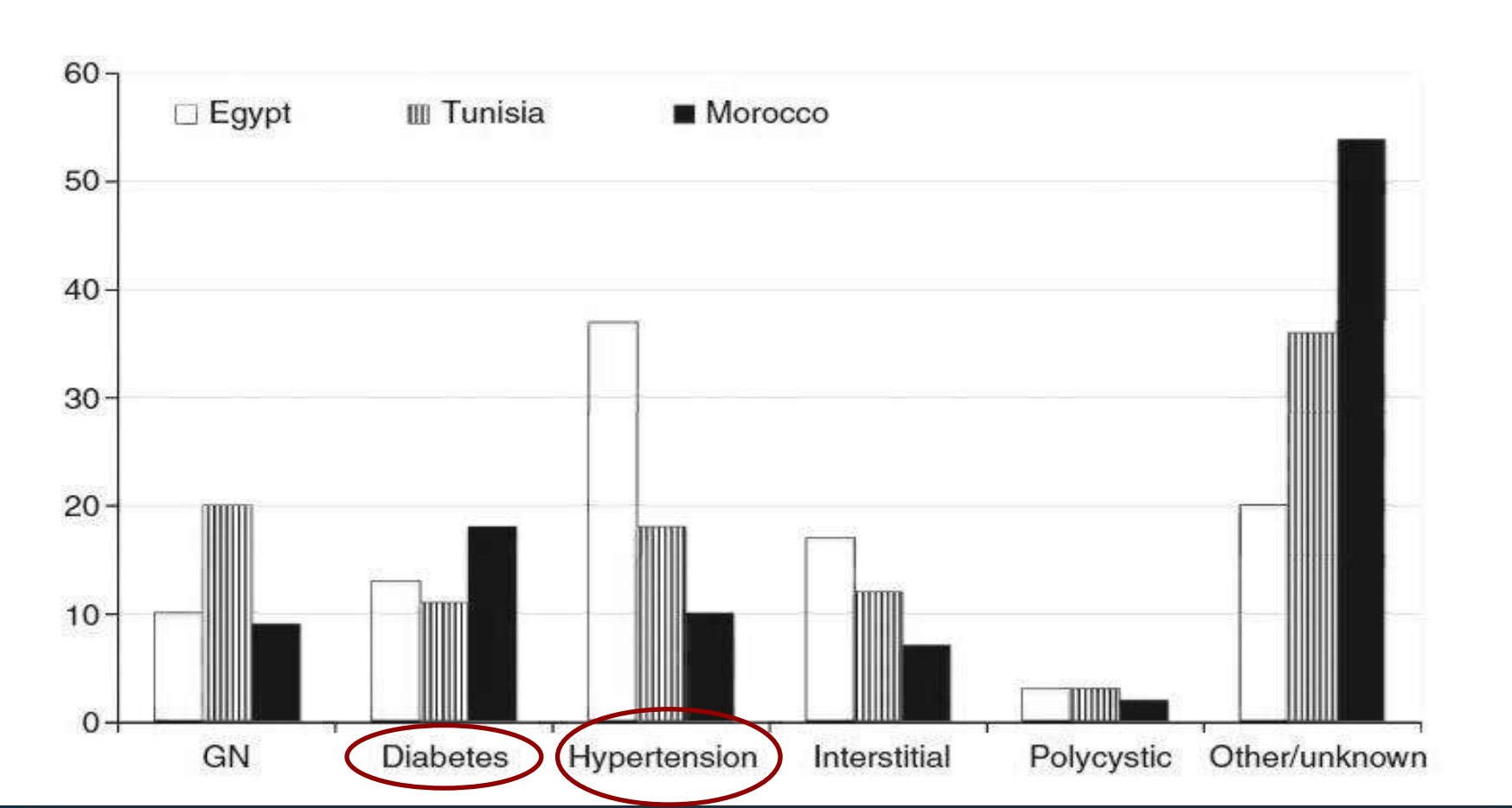
Rashad S. Barsoum[1]

[1]Kasr El-Eini Medical School, Cairo University, Cairo, Egypt

Kidney International Supplements (2013) **3**, 164–166; doi:10.1038/kisup.2013.5

KEYWORDS: CKC burden; CKD screening; developing world; glomerulonephritis; tropical nephrology

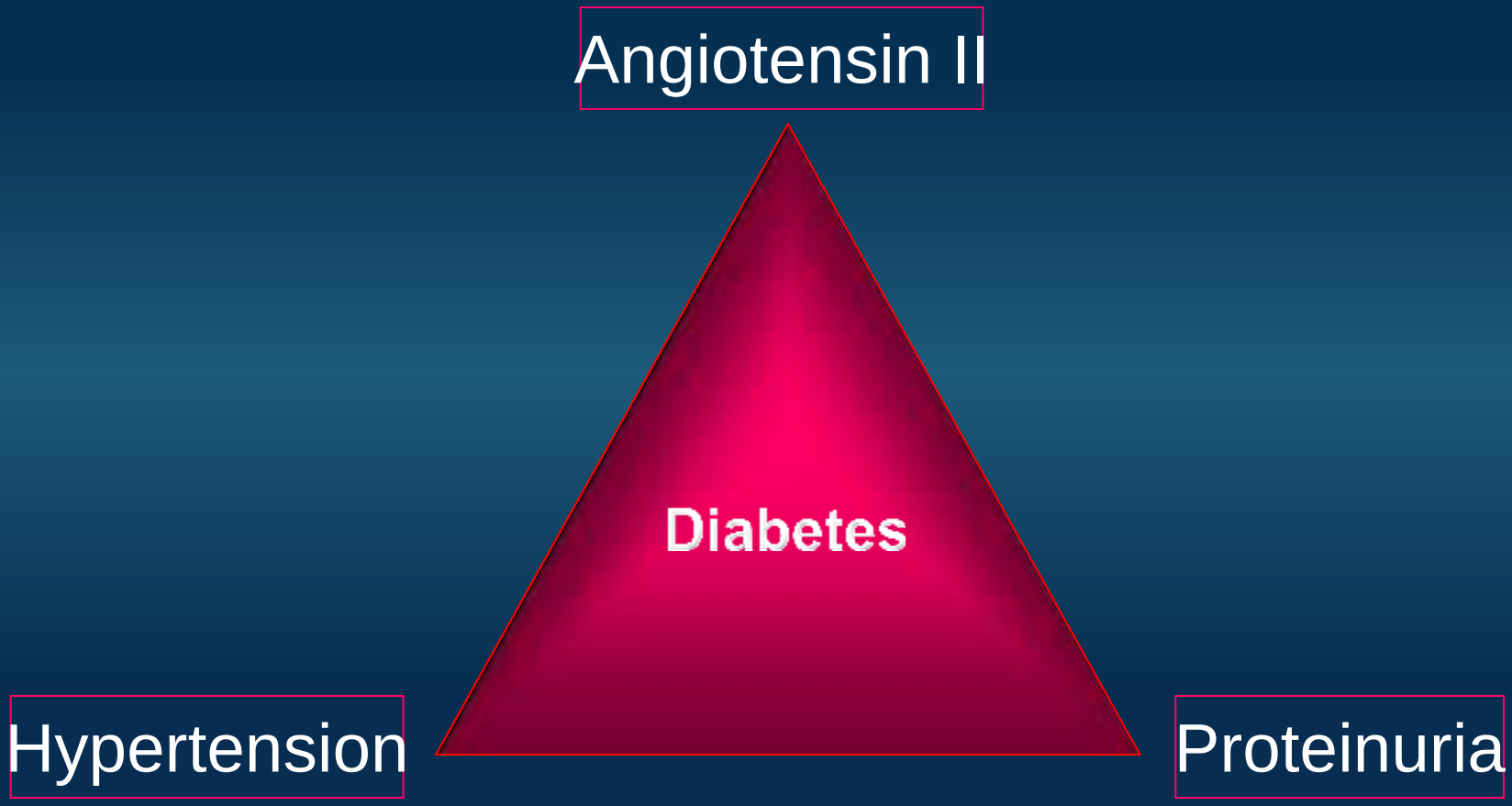
Current proportional contribution of the most common causes of ESRD in North African countries



GN: Glomerulonephritis

Rashad S. Barsoum. Kidney International Supplements (2013) 3, 164–166

The Renal Injury Triad



CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

- CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA).

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range			Persistent albuminuria categories Description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30-[illegible] g/g 3-[illegible] mmol	>300 >30 [illegible]
G1	Normal or high	≥90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29			
G5	Kidney failure	<15			

Previously micro-albuminuria

Previously macro-albuminuria

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:136-150. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf Accessed February 26, 2013

Chronic kidney disease (CGA stages)

	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative GN; focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

ADA 2014: Definitions of Abnormalities in Albumin Excretion

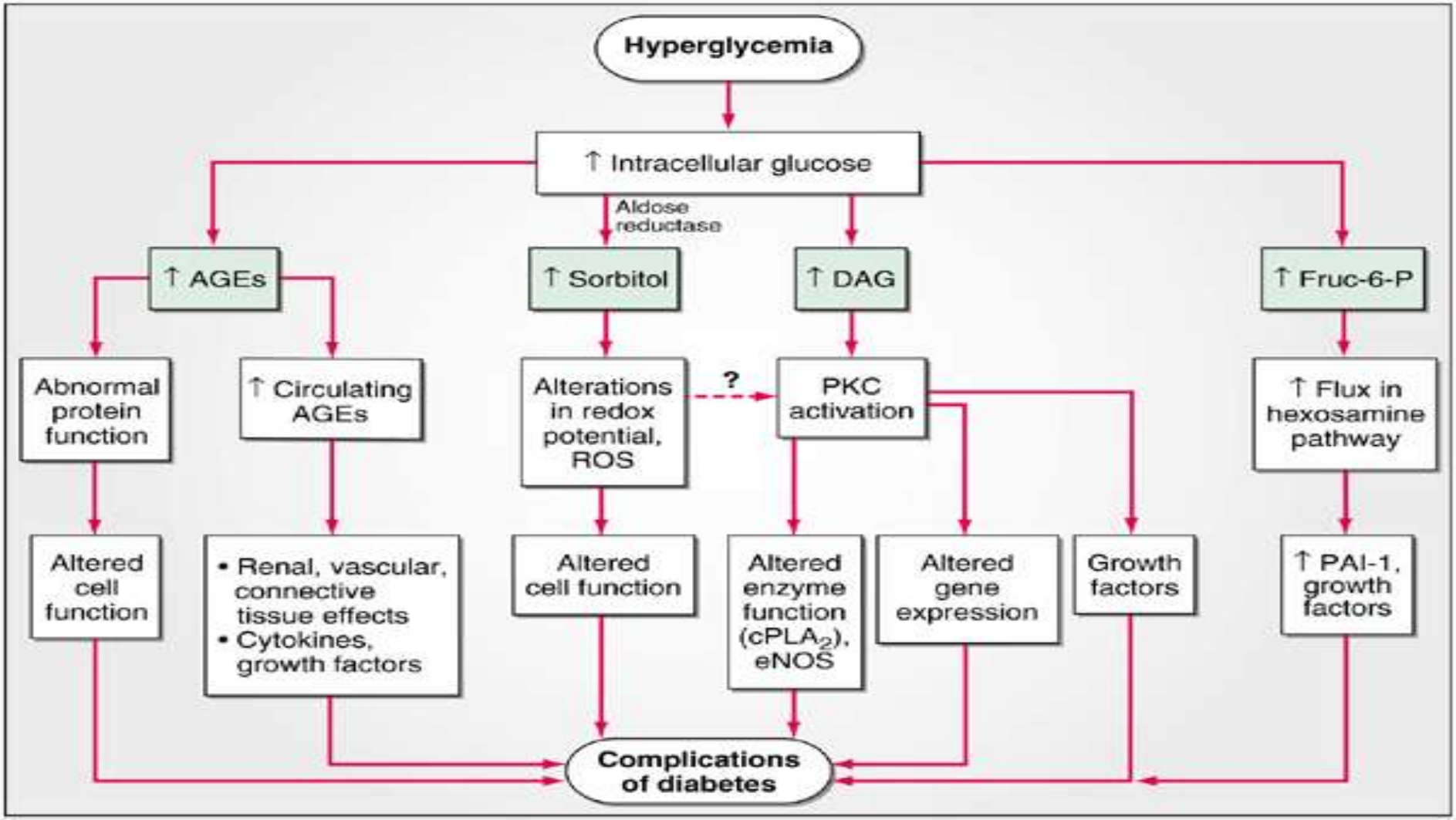
Category	Spot collection (µg/mg creatinine)
Normal	<30
Increased urinary albumin excretion*	≥30

*Historically, ratios between 30 and 299 have been called microalbuminuria and those 300 or greater have been called macroalbuminuria (or clinical albuminuria).

American Diabetes Association.

ADA. VI. Prevention, Management of Complications. Diabetes Care 2014;37(suppl 1):S44; Table 11

Possible molecular mechanisms of diabetes-related complications



Harrison's Principles of Internal Medicine, 16th Edn

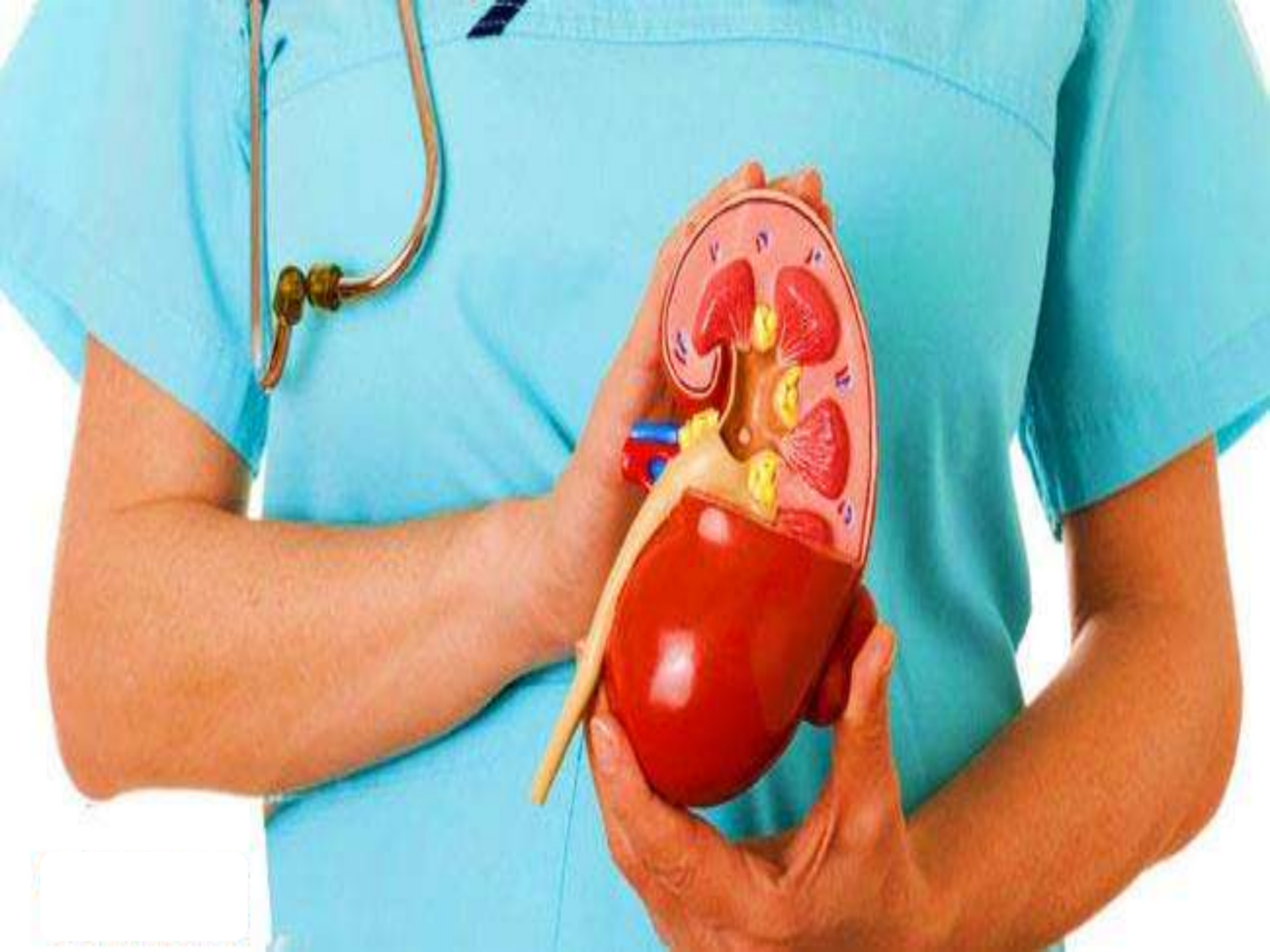
Definitions :

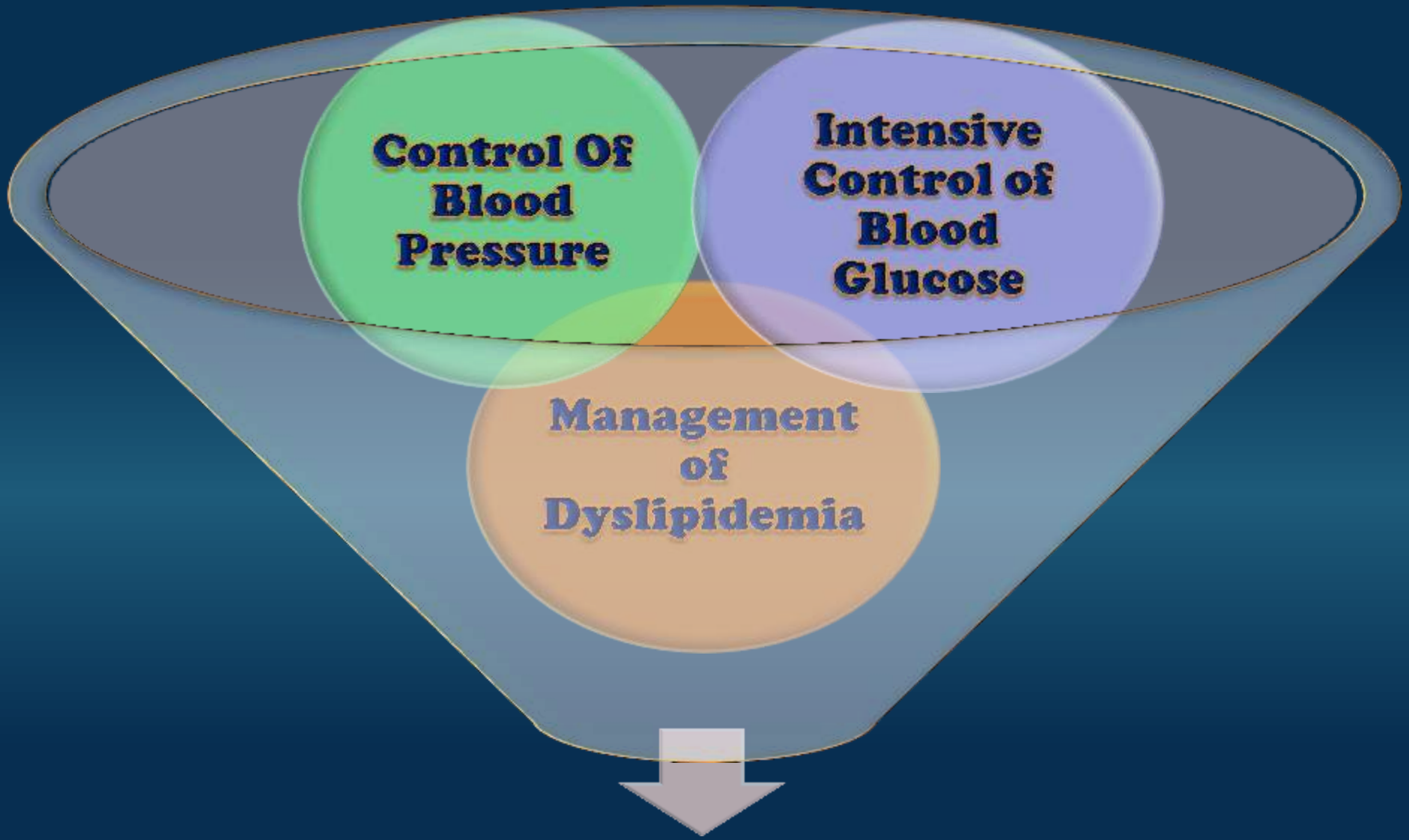
RIFLE Criteria for AKI

	GFR criteria	UOP criteria	
Risk	↑SCr x1.5 or GFR↓ >25%	UOP < .5ml/kg/h for 6 hrs	High sensitivity
Injury	↑SCr x2 or GFR↓ >50%	UOP < .5ml/kg/h for 12 hrs	
Failure	↑SCr x3 or GFR↓ >75%	UOP < .5ml/kg/h for 24 hrs or anuria for 12 hrs	High specificity
Loss	Persistent ARF = complete loss of kidney function > 4 weeks		
ESRF	ESRF > 3 months		

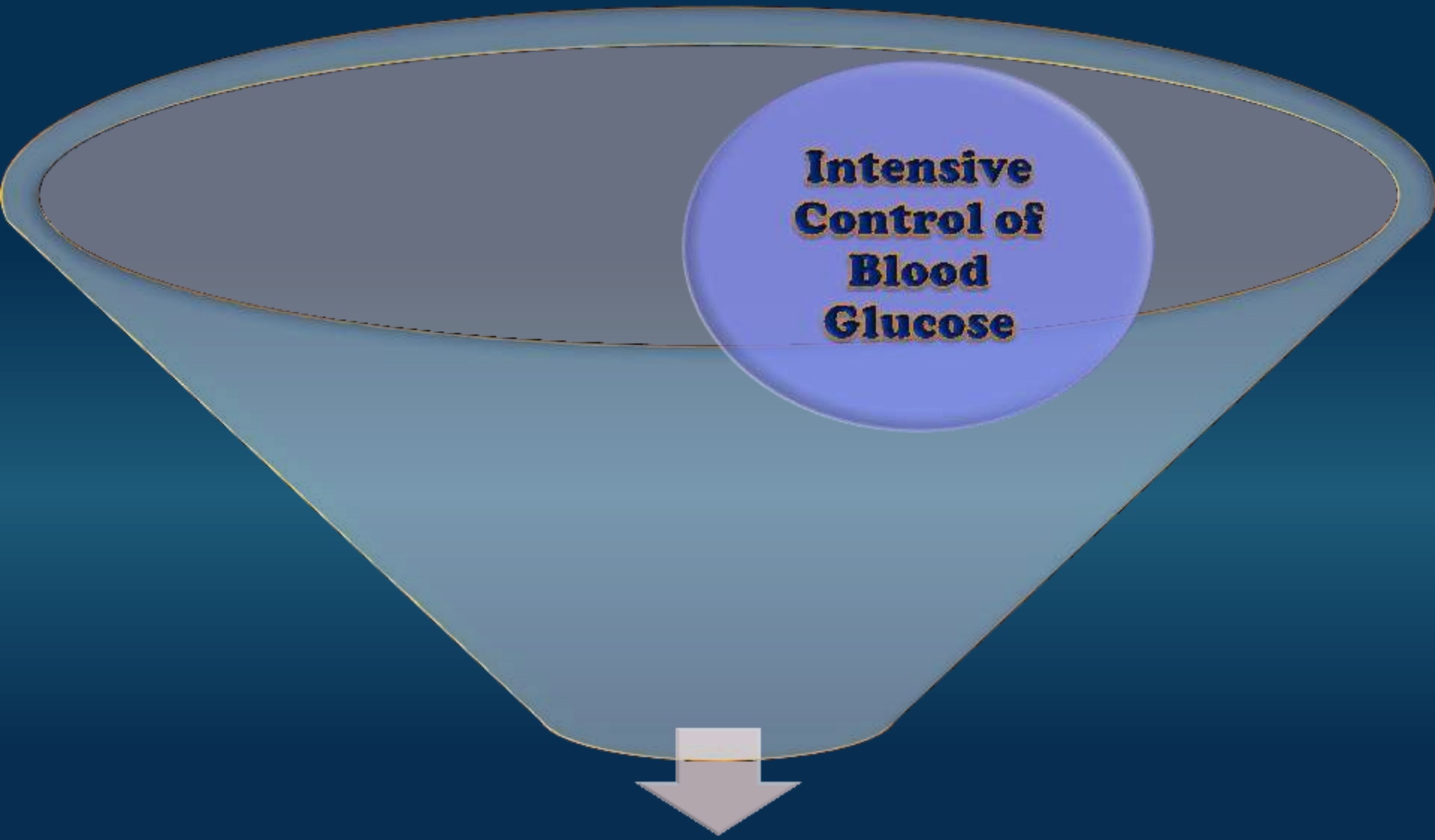
So How Big Is The Risk In Diabetes?

Avoiding AKI In Diabetes :





Management of CKD in Diabetics


Intensive
Control of
Blood
Glucose

The Evidence Confirms That:

(UKPDS, DCCT) demonstrated consistent major salutary effects of intensive therapy on microvascular complications compared with conventional therapy

Moreover, long-term follow-up of the DCCT and UKPDS cohorts has shown durable effects of early intervention

Nathan DM. Arch Intern Med. 2012 May 28;172(10):769-70.

New era in management of CKD in patients with diabetes

Better glycemic and blood pressure control

Older oral hypoglycemic agents is either contraindicated or requires dosage adjustment in CKD

New medications for diabetes have been approved recently and many can be used safely in patients with CKD

CKD: Chronic Kidney Disease.

Jindal A, et al. Endocrinol Metab Clin North Am. **2013 Dec**;42(4):789-808

Use of conventional antidiabetic medications in T2DM with CKD

Table 2 Use of conventional antidiabetic drugs in type 2 diabetic patients with chronic kidney disease

	eGFR >60 mL/min	eGFR 30–59 mL/min	eGFR <30 mL/min	Dialysis
Insulin	✓	✓	✓ dose reduction	✓ dose reduction
Metformin	✓	✓ caution	⊘	⊘
Sulfonylureas	✓	caution	caution	⊘
Metiglinides	✓	✓ caution	caution	⊘
Thiazolidinediones	✓	✓ caution	✓ caution	✓ caution
Alpha-glucosidase inhibitors	✓	✓	⊘	⊘

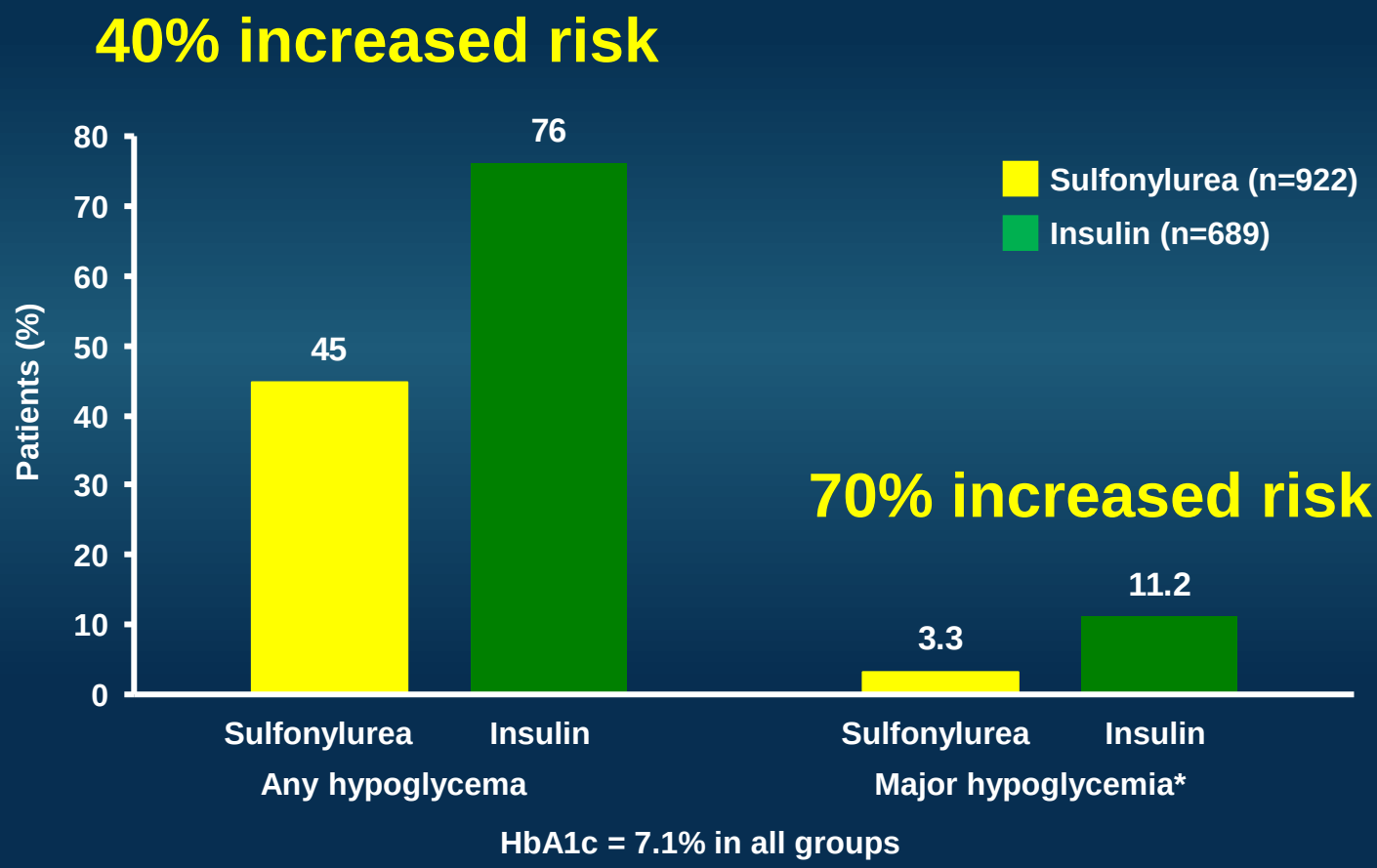
Note: ⊘, use not allowed.

Abbreviation: eGFR, estimated glomerular filtration rate.

Russo E, et al. Diabetes Metab Syndr Obes. 2013; 6: 161–170.

The risk of hypoglycemia with Insulin limits its effectiveness

Cumulative Incidence of Hypoglycemia in T2DM over 6 Years in UKPDS



HbA1c = 7.1% in all groups

SUs=sulfonylureas; T2DM=type 2 diabetes melllitus; *Requiring medical assistance or hospital admission

UK Prospective Diabetes Study Group. Diabetes.1995;44:1249–1258.

Renal impairment is a well recognized predisposing factor to hypoglycemia

40-50% of insulin is metabolized by the kidney

Accumulation of hypoglycemic agents

Small part of gluconeogenesis occurs in the kidney

Russo E, et al. Diabetes Metab Syndr Obes. 2013; 6: 161–170.
http://www.medscape.org/viewarticle/437273
http://www.elmhurst.edu/~chm/vchembook/604glycogenesis.html

Accordingly, Recommended Goals for Management of Hyperglycemia

~7.0%

to prevent or delay progression of the microvascular complications of diabetes, including DKD

NOT <7.0%

in patients at risk of hypoglycemia.

>7.0%

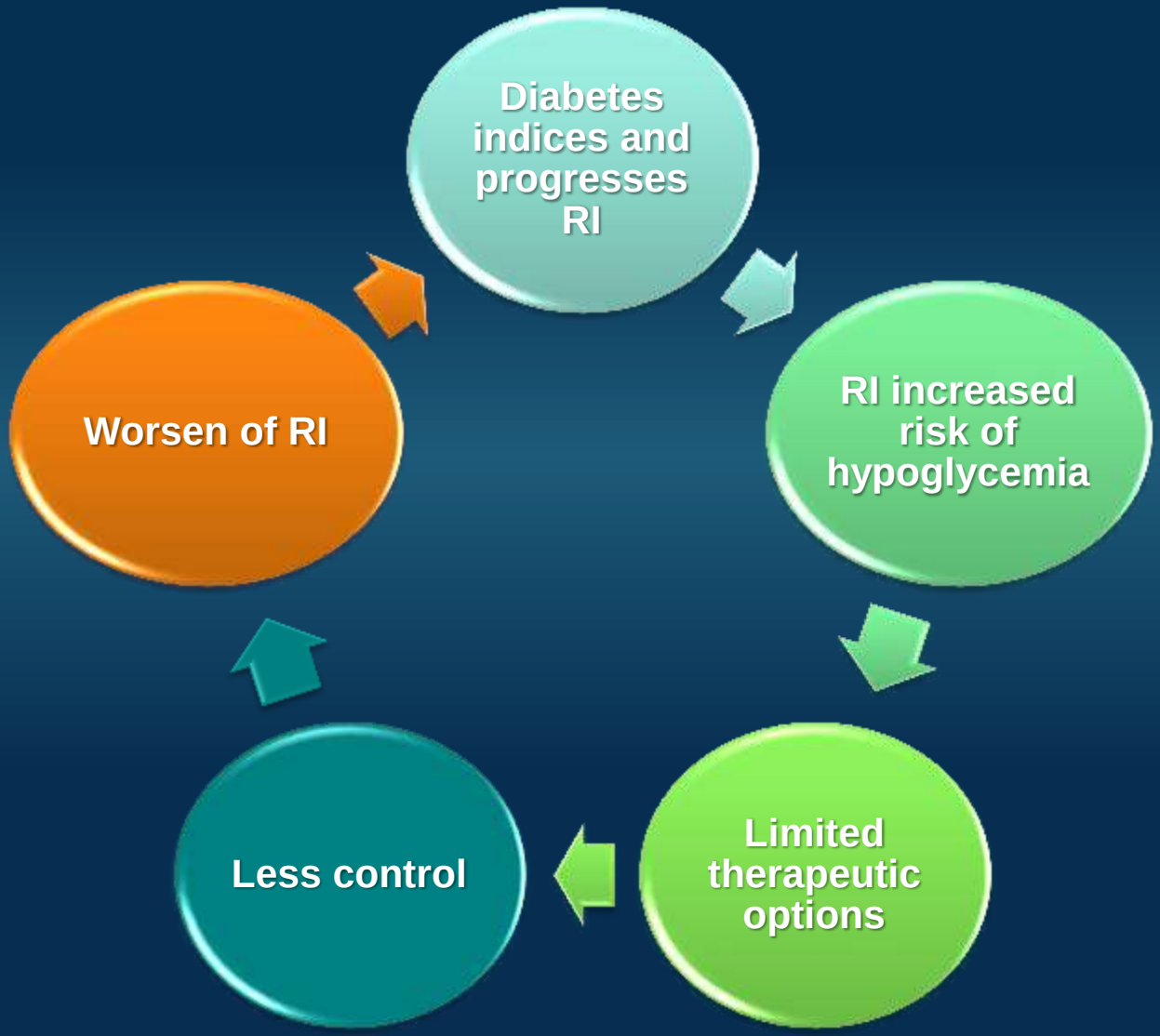
In individuals with co-morbidities or limited life expectancy and risk of hypoglycemia

HbA1c Target

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

National Kidney Foundation® KDOQI

The vicious circle leads to worsen of RI



Adapted from: Jindal A, et al. Endocrinol Metab Clin North Am. **2013 Dec**;42(4):789-808

So, Effective Management of CKD in Diabetics

- **Intensive** control of **blood glucose**
- Control of **blood pressure**
- Treatment with **ACEi or ARBs**
- **Multifactorial interventions** including a combination of improved glucose control, blood pressure control, lipid lowering, aspirin, smoking cessation, exercise programs and dietary intervention

NICE Diabetes with Kidney Disease: Key Facts MARCH 2011

KDOQI Diabetes Guideline 2012

DPP-4 Inhibitors Dose Adjustment in Renal Impairment Patients

DPP-4 Inhibitor	
Sitagliptin	GFR >50 ml/min/1.73 m² : 100 mg daily GFR 30-50 ml/min/1.73 m² : 50 mg daily GFR <30ml/min/1.73 m² : 25 mg daily
Saxagliptin	GFR >50 ml/min/1.73 m² : 5 mg daily GFR ≤50ml/min/1.73 m² : 2.5 mg daily
Linagliptin	No dose adjustment
Vildagliptin	GFR ≥50 ml/min/1.73 m² : 50 mg twice daily GFR <50 ml/min/1.73 m² : 50 mg once daily

Which is available dosing.

National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.

National Kidney Foundation®
KDOQI

MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Novartis drug Galvus® approved in EU for type 2 diabetes patients with moderate or severe renal impairment with limited treatment options

Basel, December 05, 2011 ·

original article

Diabetes, Obesity and Metabolism 13: 947–954, 2011.

Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial

V. Lukashevich[1], A. Schweizer[2], Q. Shao[1], P.-H. Groop[3,4] & W. Kothny[1]

ORIGINAL ARTICLE

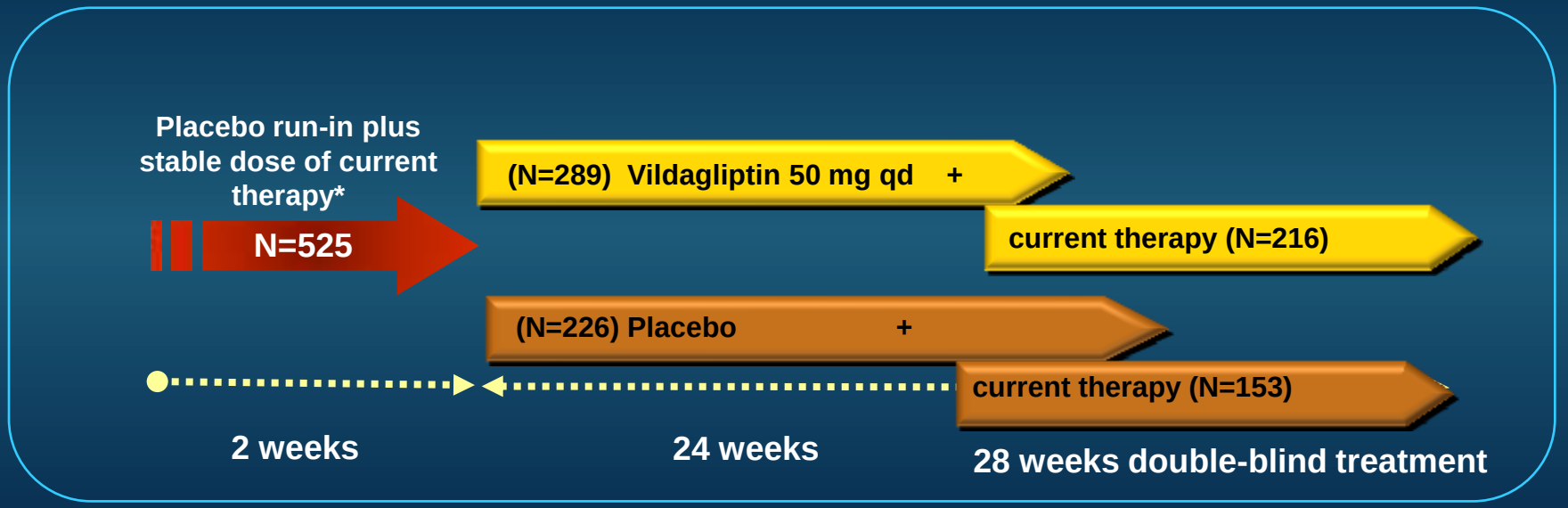
original article

Diabetes, Obesity and Metabolism 2012.

One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment

Study objective and design...

To assess long-term safety and efficacy of vildagliptin (50 mg qd) in patients with T2DM and moderate or severe renal impairment (RI)



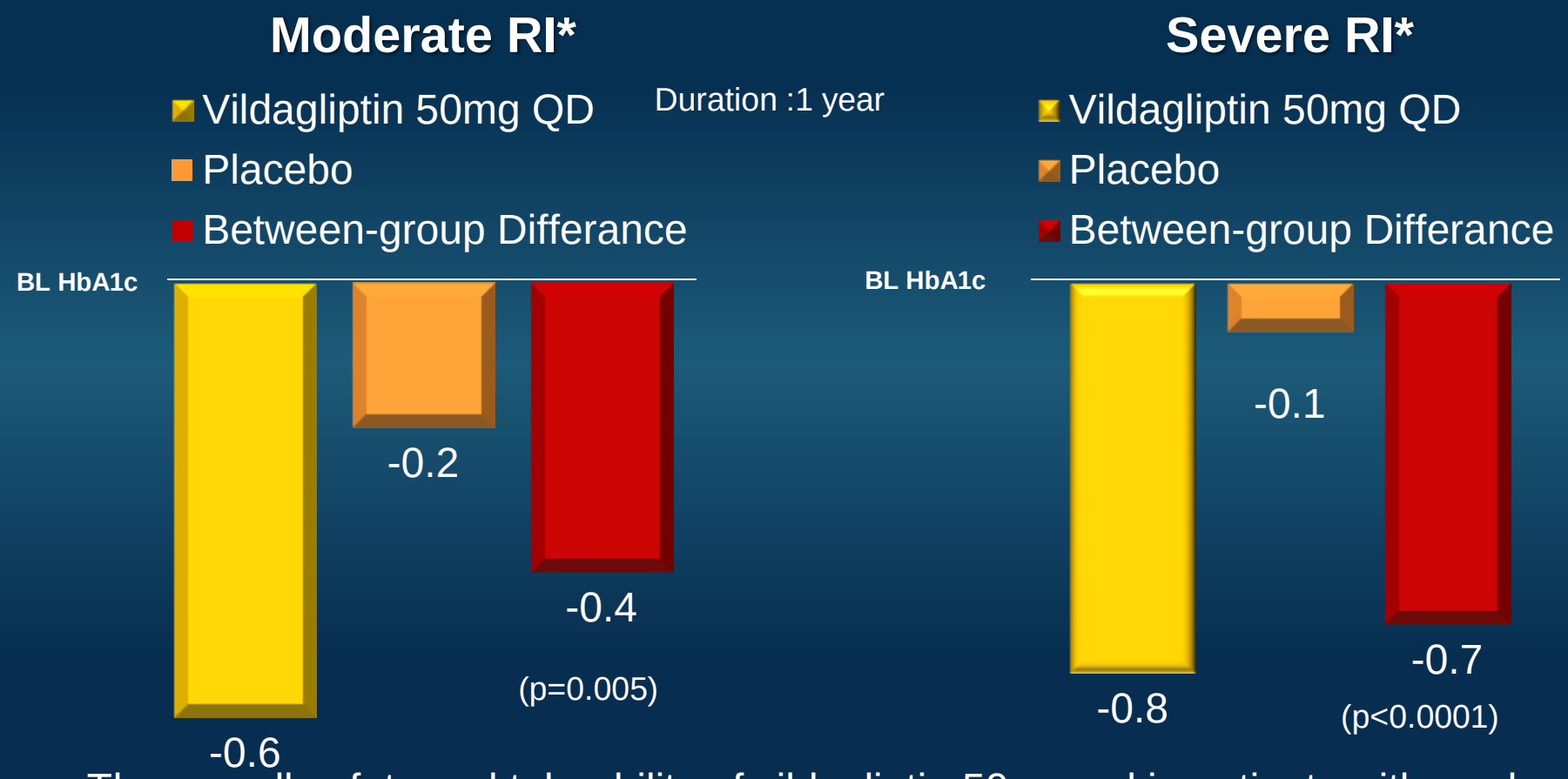
*Randomized: patients must remain on their current anti-diabetic therapy (stable dose for at least 4 weeks prior to visit 1) or remain untreated for the duration of the study if patient is not on anti-diabetic therapy at study entry (unless patient meets criteria for rescue medication).
Total of 525 includes 10 patients with mild RI revealed during reclassification by MDRD method: 7 were randomized to vildagliptin, 3 to placebo, but data from mild RI patients are not reported

1) Primary objective = safety and tolerability
2) Secondary objective = efficacy

Adapted from Lukashevich V et al. Diabetes Obes Metab. 2011; 13:947-954
Adapted from W. Kothny,et al. Diabetes Obes Metab. *May 2012*

Vildagliptin once daily:

Effective in reducing the HbA1c in moderate and severe RI patients



The overall safety and tolerability of vildagliptin 50 mg qd in patients with moderate or severe RI was comparable with that of placebo.

Adapted from W. Kothny,et al. Diabetes Obes Metab. *May 2012*

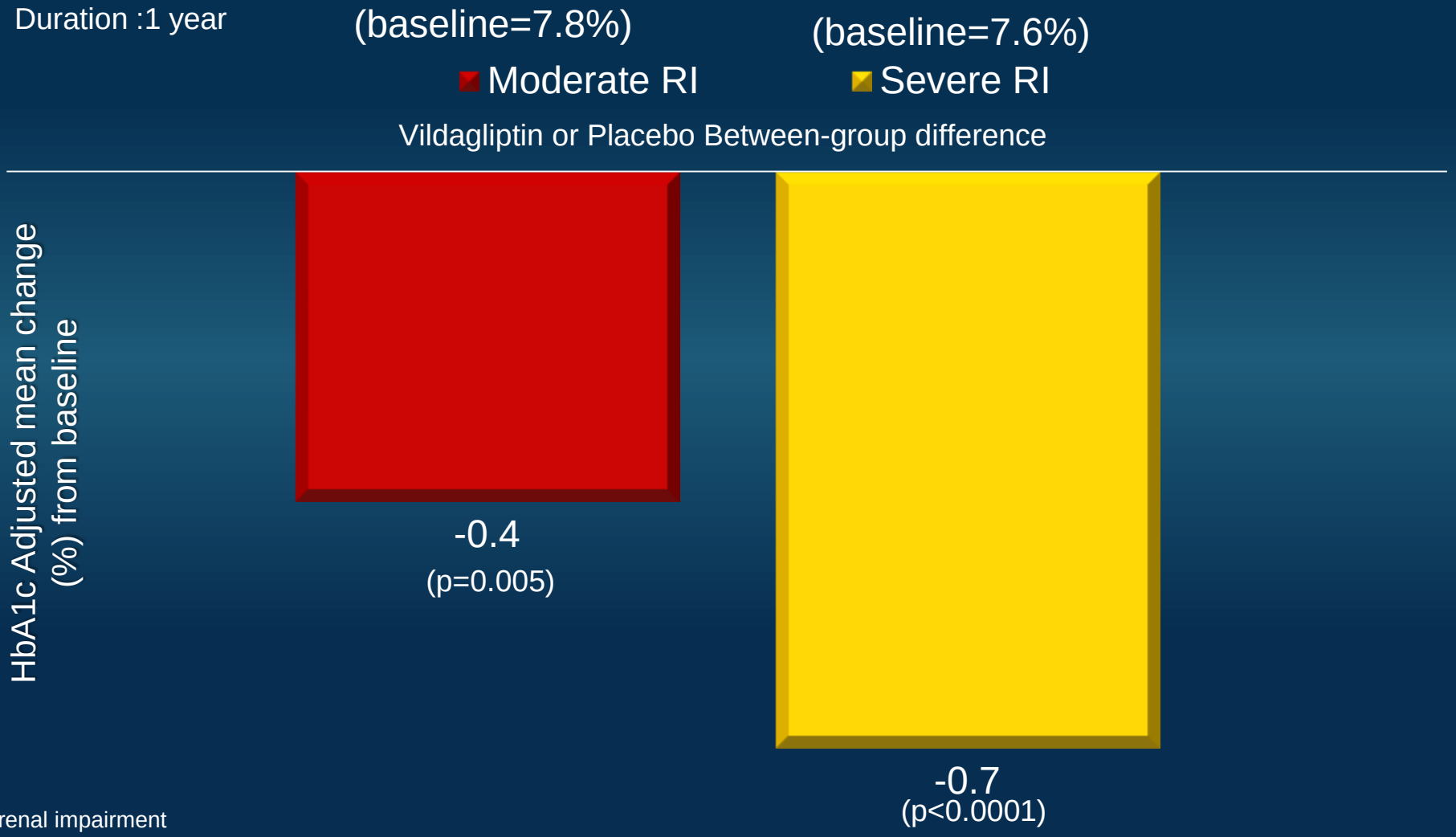
RI: renal impairment

*Baseline in moderate and severe RI patient was 7.8% and 7.7% respectively

Vildagliptin once daily:

is safe and effective treatment for moderate and severe diabetic RI patients

Duration :1 year



RI: renal impairment
Baseline in moderate and severe RI patient was 7.8% and 7.7% respectively

Adapted from W. Kothny,et al. Diabetes Obes Metab. *May 2012*

Vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo

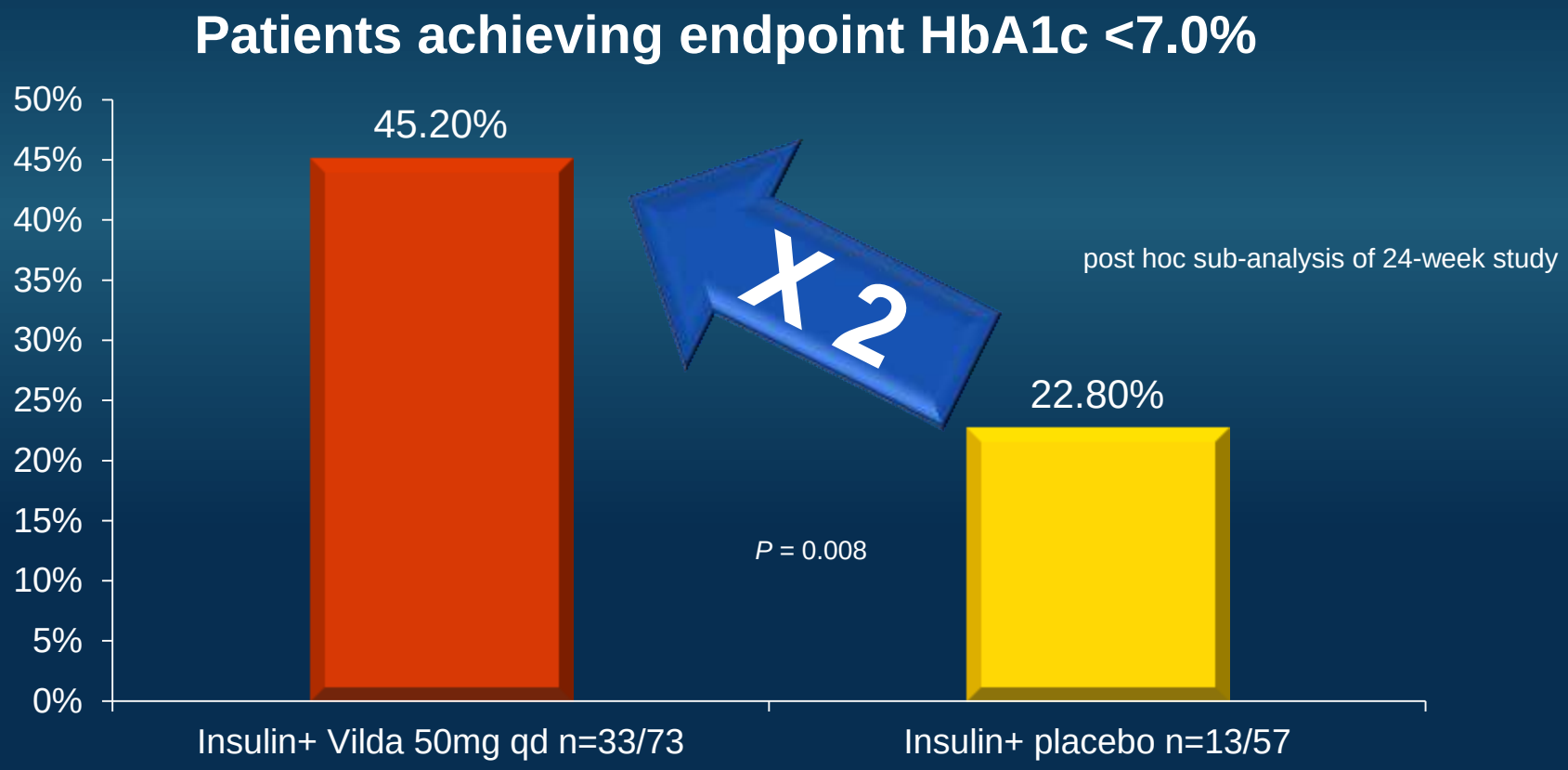
	Moderate RI [n (%)]		Severe RI [n (%)]	
Event category	Vildagliptin 50 mg qd (N=122)	Placebo (N=89)	Vildagliptin 50 mg qd (N=94)	Placebo (N=64)
Any adverse event	103 (84.4)	76 (85.4)	80 (85.1)	56 (87.5)
Any serious adverse event	26 (21.3)	17 (19.1)	23 (24.5)	16 (25.0)
Any adverse event leading to discontinuation	6 (4.9)	5 (5.6)	9 (9.6)	4 (6.3)

RI, renal impairment

Adapted from W. Kothny,et al. Diabetes Obes Metab. *May 2012*

In patients with severe renal impairment more Patients achieved the glycemic goal with Vildagliptin/insulin combination

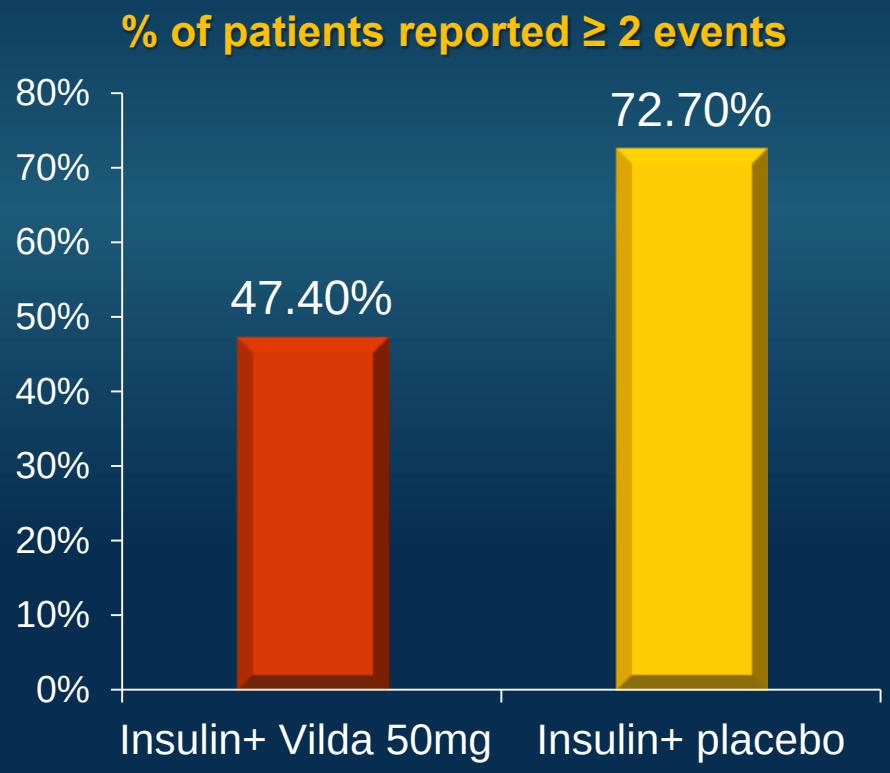
The percentage of patients achieving endpoint HbA1c <7.0% in the vildagliptin group (33/73 patients, 45.2%) was twice that in the placebo group (13/57 patients, 22.8%, *P* = 0.008).

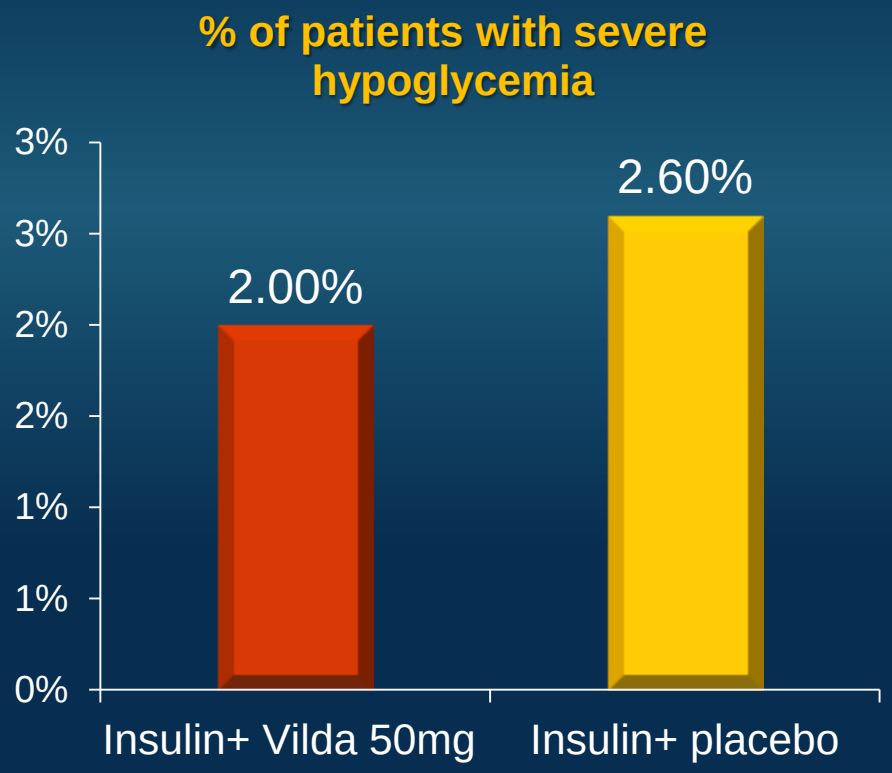


Lukashevich V, et al. Vasc Health Risk Manag. 2013;9:21-8.

Less patients experienced ≥ 2 hypoglycemic events

- A higher % of patients reported ≥ 2 events (72.7% with placebo versus 47.4% with vildagliptin).
- Severe hypoglycemia was reported at a similarly low rate in the two groups (2.0% with vildagliptin and 2.6% with placebo).





Lukashevich V, et al. Vasc Health Risk Manag. 2013;9:21-8.

post hoc subanalysis of 24-week study

What About Other Adverse Events?

The overall adverse event profile was also similar in the two treatment groups, and there were no notable differences in the subgroup of insulin-treated patients with severe renal impairment compared with the overall study population that was previously reported. The percentage of patients receiving

Lukashevich V, et al. Vasc Health Risk Manag. 2013;9:21-8.

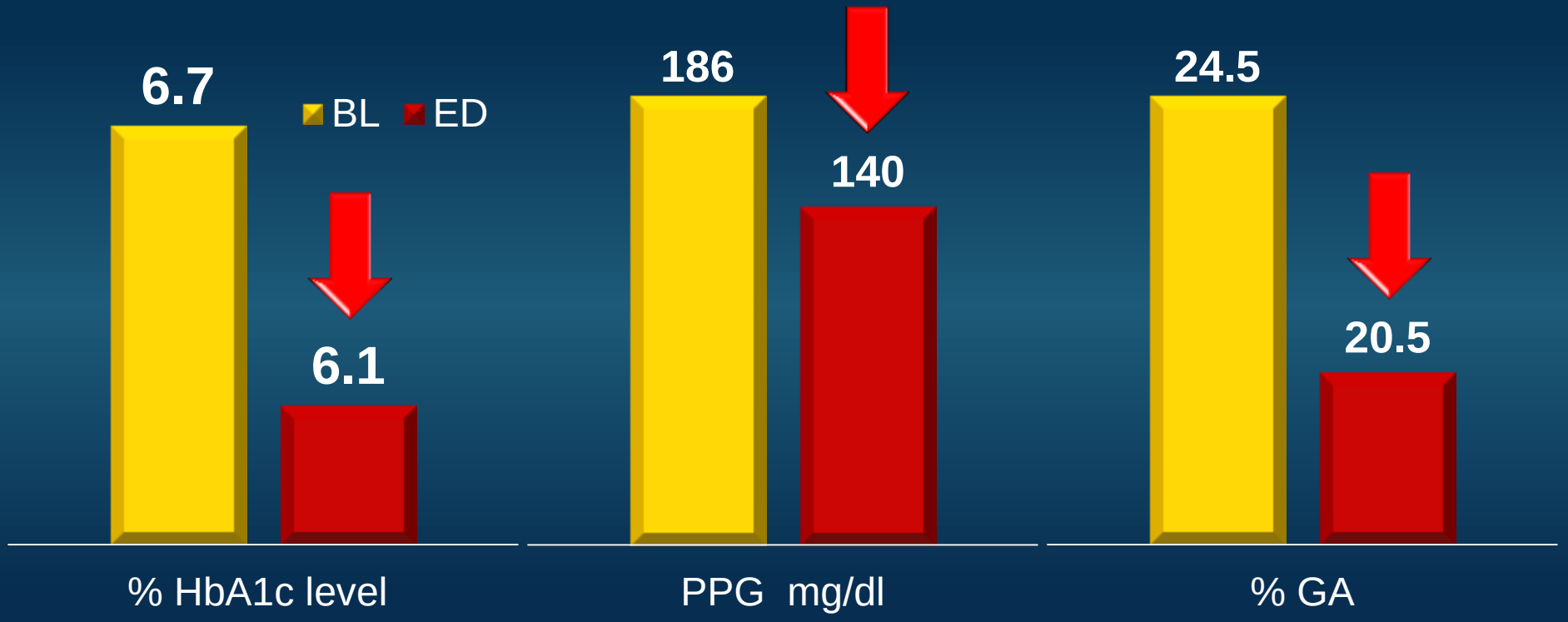
Advance Publication
doi: 10.1507/endocrj. EJ11-0025

ORIGINAL

The dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin improves glycemic control in type 2 diabetic patients undergoing hemodialysis

Midori Ito[1)], Masanori Abe[1)], Kazuyoshi Okada[1)], Hirokazu Sasaki[1)], Noriaki Maruyama[1), 3)], Masaaki Tsuchida[4)], Terumi Higuchi[5)], Fumito Kikuchi[6)] and Masayoshi Soma[1), 2)]

Vildagliptin is an effective treatment in glycemic management in HD patients



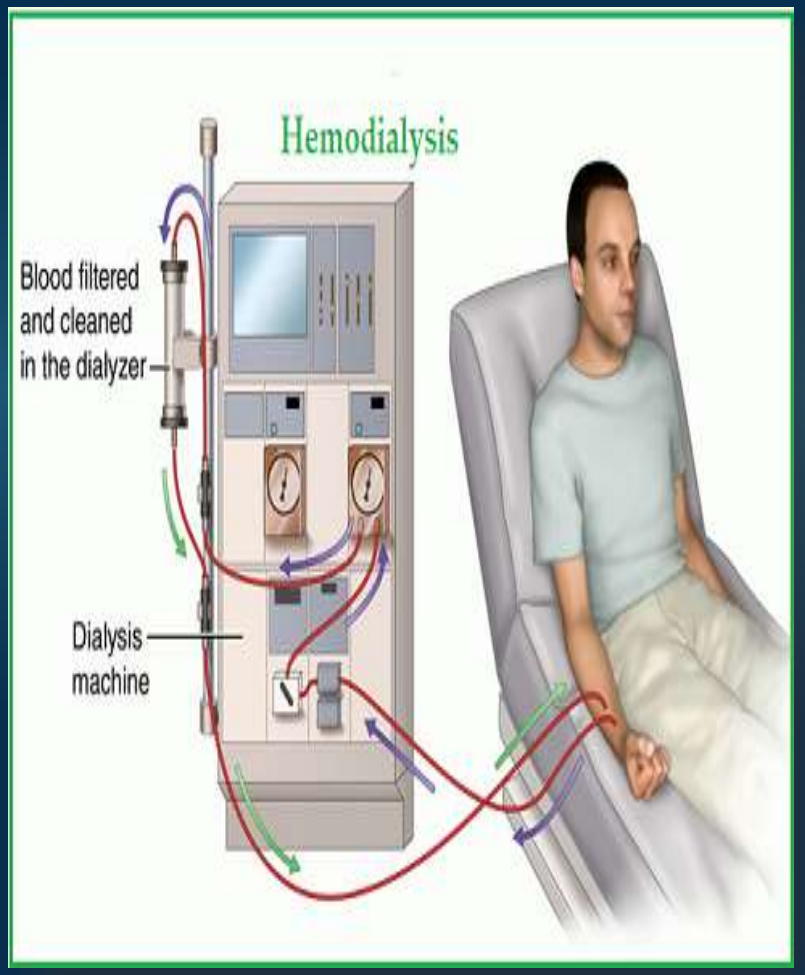
Duration :24 weeks

HD: Hemodialysis, BL Baseline, ED: Endpoint, PPG: postprandial plasma glucose, GA: glycated albumin

Ito *et al.* Efficacy of vildagliptin in HD patients *Endocrine Journal 2011,* ***58 (11), 979-987***

Safety is well established with vildagliptin with type 2 diabetic patients undergoing Hemodialysis

- No serious adverse effects such as hypoglycemia or liver impairment were observed in any patient.
- Vildagliptin was effective as a treatment for diabetic patients undergoing HD.



HD: Hemodialysis

Ito *et al.* Efficacy of vildagliptin in HD patients *Endocrine Journal 2011*, ***58 (11), 979-987***

Vildagliptin showed significant reduction from baseline in HbA1c & 2HPG in KTRs with overt NODAT

Haidinger et al

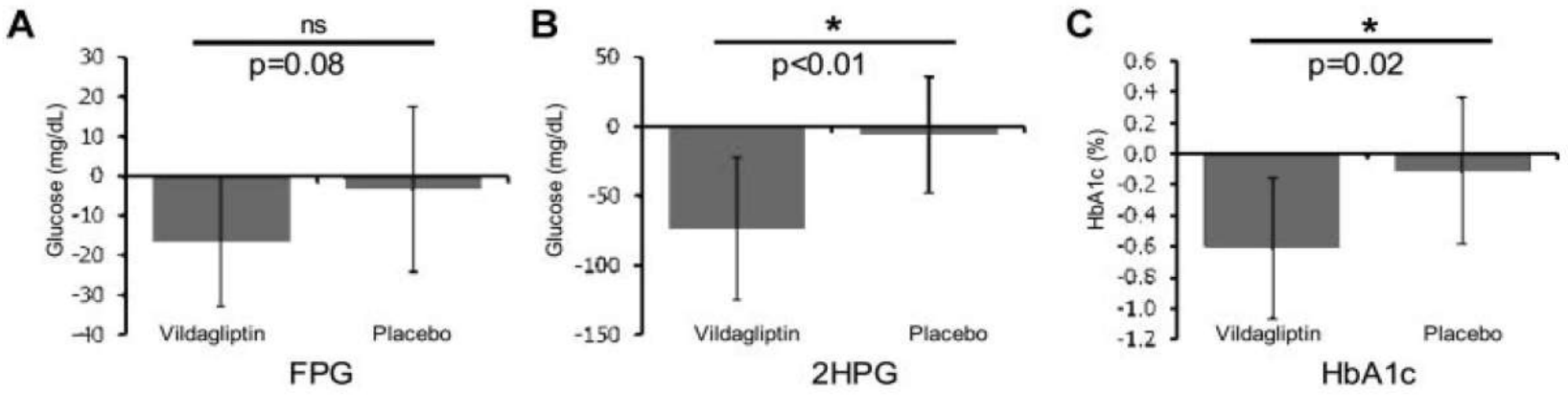


Figure 2: Intraindividual differences in metabolic parameters from baseline to 3 months between the vildagliptin and placebo groups. Mean differences ± SD between baseline and 3 months are shown for patients in the vildagliptin and placebo group for (A) fasting plasma glucose (FPG; $p = 0.08$); (B) 2-h plasma glucose (2HPG; $p < 0.01$); (C) HbA1c ($p < 0.02$). The asterisk indicates findings with $p < 0.05$.

DPP-4 inhibition with Vildagliptin in KTRs with overt NODAT was safe and efficient, providing a novel treatment alternative for this specific form of diabetes.

HbA1c: Glycated Hemoglobin, 2HPG: 2 hour plasma glucose,KTRs: Kidney Transplanted Recipients, NODAT: New Onset Diabetes After Transplantation. KTRs: Kidney Transplanted Recipients, NODAT: New Onset Diabetes After Transplantation.

Haidinger M, et al. Am J Transplant. 2013 Nov 26 [Epub ahead of print] Novartis is not recommending indications outside the approved BPI in Egypt"

Referring to Galvus® Prescribing Information:

Galvus ® is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.


10 METER

Review Article

Hong Kong J Nephrol • April 2011 • Vol 13 • No 1

Novel Drug Treatment for Diabetic Nephropathy

Amitabh Dash,[1] Rituparna Maiti,[2] Tejaswi Kumar Akantappa Bandakkanavar,[1] Bajrang Lal Pandey[1]

- ***Ruboxistaurin*: Protein kinase C inhibitor**
  - an orally active selective inhibitor of the β-isoform of PKC
  - reduces the actions of vascular endothelial growth factor (VEGF)
  - attenuates the progression of diabetic retinopathy
  - normalize glomerular hyperfiltration
  - reduce TGF-β levels and proteinuria

Review Article

Hong Kong J Nephrol • April 2011 • Vol 13 • No 1

Novel Drug Treatment for Diabetic Nephropathy

Amitabh Dash,[1] Rituparna Maiti,[2] Tejaswi Kumar Akantappa Bandakkanavar,[1] Bajrang Lal Pandey[1]

- ***Rapamycin (sirolimus): m-TOR inhibitor***
  - systemic administration of rapamycin, a systemic and potent inhibitor of mTOR, markedly ameliorated pathological changes and renal dysfunction in Diabetic db/db mice as a model of ESRD associated with DN
  - Sirolimus lowered the expression and activity of glomerular TGF-β and VEGF

Review Article

Hong Kong J Nephrol • April 2011 • Vol 13 • No 1

Novel Drug Treatment for Diabetic Nephropathy

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- ***Pentoxifylline***
  - Pentoxifylline administration has prevented Renal expression of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6
  - Pentoxifylline treatment caused regression and prevented the progression of renal damage

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- ***Advanced glycation end-products inhibitor***
  - 1) AGE formation inhibitor: ARBs, R-147176, aminoguanidine, benfotiamine, pyridoxamine
  - 2) AGE cross-link breaker (alagebrium)
  - 3) RAGE antagonist (PPAR-γ antagonists)
  - 4) AGE binder (Kremezin)
  - 5) hypoxia-inducible factor (HIF) activator

Thank You